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Review

Genetics of Human Social Behavior

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Human beings are an incredibly social species and along with eusocial insects engage in the largest cooperative living groups in the planet's history. Twin and family studies suggest that uniquely human characteristics such as empathy, altruism, sense of equity, love, trust, music, economic behavior, and even politics are partially hardwired. The leap from twin studies to identifying specific genes engaging the social brain has occurred in the past decade, aided by deep insights accumulated about social behavior in lower mammals. Remarkably, genes such as the arginine vasopressin receptor and the oxytocin receptor contribute to social behavior in a broad range of species from voles to man. Other polymorphic genes constituting the "usual suspects"—i.e., those encoding for dopamine reward pathways, serotonergic emotional regulation, or sex hormones—further enable elaborate social behaviors.

Introduction

> *"Society is a masked ball, where everyone hides his real character, and reveals it by hiding."* —Ralph Waldo Emerson

Human beings spend most of their time in society surrounded by other human beings, and a good deal of this time is occupied in exchanging signals—verbal and nonverbal—with each other. Indeed, there is considerable evidence that the increasing complexity of the social milieu, rather than measures of environmental complexity, is the driving force of primate brain size (Byrne and Bates, 2007). Our multifaceted lives include behaviors by which we synchronize social interactions and duties, actions such as securing a mate, parenting, aggression, altruism, and recognition of rank. Underlying most of these behaviors are a bevy of social cognitions and emotions, ranging from love, empathy, moral sense, and trust to political attitudes and instrumental goals. In order to attain social goals and bridge the gap between cognition, emotion, and behavior, humans have developed a set of complex social skills. For example, as the ever more sophisticated demands of group living have required individuals to acquire resources not only by cunning, but also by cooperation, Machiavellian Intelligence—the capacity to politically engage within a social group—is likely to have played a part in hominid evolution. Social memory—the capacity to remember encounters and perceive dominance hierarchies—is another crucial element of social life (Dunbar, 2003). Humans also possess Theory of Mind, the ability to put oneself into someone else's shoes, to imagine their thoughts and feelings (Baron-Cohen et al., 1985). Altogether, the intricacies of human society require considerable levels of social intelligence, navigation, and manipulation; qualities that are the sine qua non of our successful "pursuit of happiness."

Some phenotypes are easy to define and study. Common illnesses are characterized by sensitive and specific laboratory-based measures. Mental illnesses present greater obstacles, reflecting the complexity of the human brain and the difficulty of quantifying thinking (especially pathological thoughts and unusual behaviors). Similarly, nonclinical behavioral phenotypes, especially those that constitute the social brain, present barriers regarding definition, measurement, and accuracy. Additionally, investigating the relative hardwiring of important everyday concepts derived from the social sciences such as marketplace behavior, life history choices, political attitudes, leadership, and popularity poses a real obstacle for the genomic sciences. To improve our understanding of the molecular genetic architecture of social cognition, the challenge of refining social phenotypes should be addressed both by modeling behavior via controlled laboratory-based experiments and by extending the robustness of these phenotypes through field experiments and survey data.

This review highlights emerging topics in the genetics of social cognition and includes a discussion of twin studies, which establish the heritability of social phenotypes, and molecular genetic studies, which seek to identify specific genes and polymorphisms contributing to individual differences. Almost all reported genetic studies of social cognition are association studies; consequently, a caveat to the reader of this review is in place. A consensus statement by the STrengthening the REporting of Genetic Association studies (STREGA) initiative (Little et al., 2009) regarding the challenges presented by such investigations focuses on main reporting issues including population stratification, genotyping errors, statistical methods, and volume of data. Its recommendations are intended to maximize the transparency, quality, and completeness of reporting of association studies. In the current review, the robustness of the cited

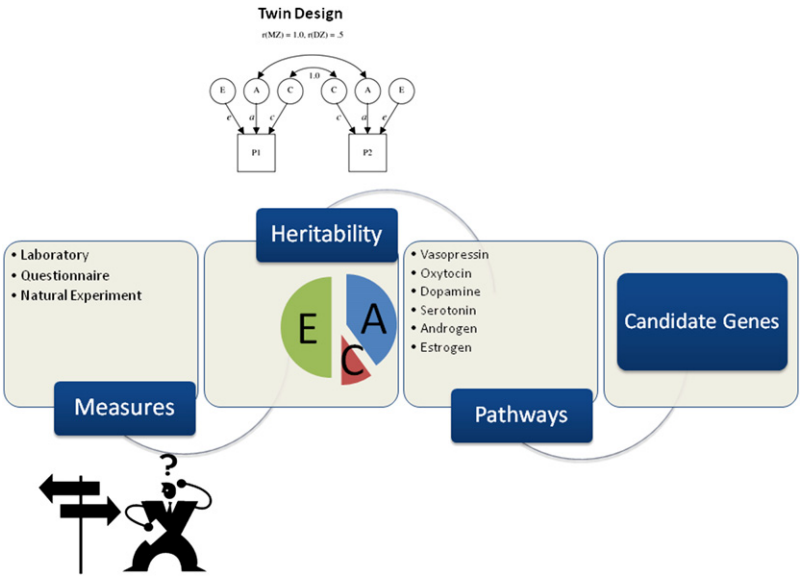

Figure 1. Pathway to Gene Discovery for Social Behaviors

In the search for social genes, the definition of phenotype is crucial. Social behaviors can be characterized by pencil and paper questionnaires, laboratory models, and natural experiments. Once the phenotype is defined, the MZ-DZ method is used to estimate the overall contribution of heredity (A: additive genetic effects) and environment (C: shared; E: nonshared). Animal models, informed hypotheses, and good hunches based on neurochemical and neuropharmacological experiments provide models of specific neurotransmitter systems that mold specific social behaviors and ipso facto suggest candidate genes.

investigations is evaluated by noting sample size, significance level, vetting in an independent sample, family-based or population-based design, and other STREGA criteria (Table S1, available online). Many of the cited studies are small, reflecting the freshness of the field, and do not live up to the new STREGA standards. Most of the studies we cite may be susceptible to the confounds of population stratification, and very few used family-based association methods, in which genetic differences *within* families are used to determine the influence of genes, thereby controlling for ethnic or cultural factors (Hamer and Sirota, 2000). Additionally, replication in independent samples is rare, and many of the studies we discuss have yet to be vetted across ethnic groups or by other investigators. Let the reader be further advised that genetic association studies for complex phenotypes are known for nonreplications (Ioannidis, 2007); nevertheless, it is encouraging that recent meta-analyses are showing significant associations with behavioral measures that stand the test of independent replication (Han et al., 2010; Kia-Keating et al., 2007; Munafò et al., 2008a; Verhagen et al., 2008).

Twin Studies

> *"My sister and I, you will recollect, were twins, and you know how subtle are the links which bind two souls which are so closely allied."* —Helen Stoner, in *The Adventure of the Speckled Band* by Sir Arthur Conan Doyle

Twin studies are the mainstay of behavioral genetics and serve as a crucial tool in establishing the heritability of phenotype. These studies have provided critical evidence that genes play a role in our ability to understand and manipulate social relationships. The most common design compares monozygotic (MZ) and dizygotic (DZ) twins raised in the same family (Figure 1). MZ twins share virtually all their genetic sequence, whereas DZ twins share approximately 50% of their genes. If we assume the environmental influences are the same for MZ and DZ twins for the phenotype of interest, then heritability is reflected in the difference in correlations between MZ twins and DZ twins. Twin similarity not accounted for by genetic effects can be attributed to the shared environment, whereas differences between twins that are not due to genetic differences are ascribed to nonshared environment or to measurement error (Plomin et al., 2008). The concept of "nonshared environmental factors" essentially includes all possible exogenous and personal events during one's lifetime that could influence the phenotype, other than genetic effects and influences shared by twins in a common family environment. Extensive studies employing the twin method have investigated the relative influence of environmental and genetic influences on social behaviors (Figures 2 and 3). Notably, although twin studies allow an overall estimate of heritability, neither the number of genes nor the effect size of each gene can be known.

Twin studies, like other methodologies, are prone to confounds that are important to be cognizant of when interpreting empirical findings, including representativeness and reciprocal influences. As discussed by Plomin et al. (2008), twins are different from singletons in at least two ways. Twins are often born 3–4 weeks prematurely and intrauterine environments can be adverse. Newborn twins are also about 30% lighter at birth than the average singleton newborn, a difference that disappears by middle childhood. Language develops more slowly and twins also perform less well on tests of verbal ability and IQ. These delays are similar for MZ and DZ twins and most of this deficit is recovered in the early school years. When studying normal individual differences, quality twin studies using large samples often screen out twins with a history of extreme pregnancy, birth, or developmental problems (Dale et al., 2000). Twins do not appear to significantly differ from singletons for phenotypes such as personality (Johnson et al., 2002) or in motor development (Brouwer et al., 2006). More importantly, the focus of twin studies is usually on parsing the variance into genetic and environmental components. Thus, even for traits in which there may be average differences between twins and singletons, there is great variability in both groups, and it may be safe to assume that the relative importance of genetics and the environment are similar in twins and singletons. Finally, the remarkable convergence of twin study results with those of adoption studies, using a very different design (Plomin et al., 2008), suggests that the main findings of twin studies are robust to the type of sample studied.

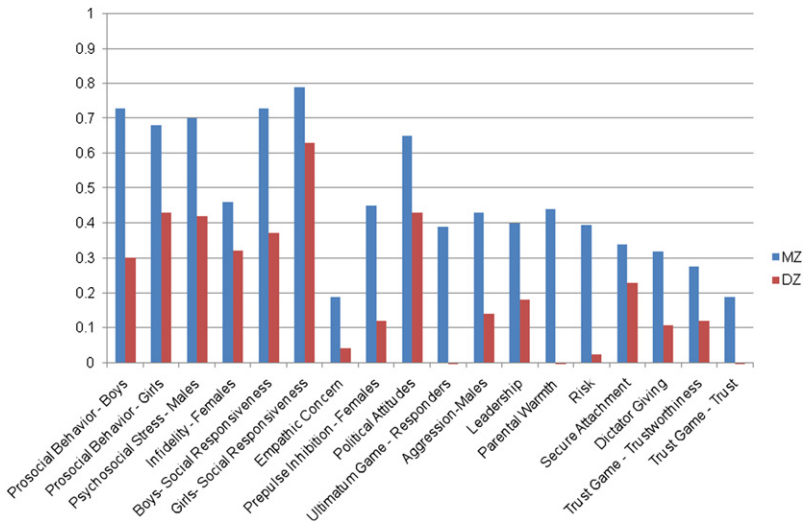

Figure 2. MZ-DZ Correlations for Social Phenotypes

Comparison of MZ and DZ correlations along a broad swath of social phenotypes. A short description and reference to all the phenotypes listed is provided in Table S2.

Current twin studies also assume similar degrees of reciprocal influences between MZ and DZ twins. If twins influence each others' choices positively through social interaction, and MZ twins interact more frequently than DZ twins, then their degree of similarity on phenotypes relevant to social cognition will be somewhat inflated (Constantino and Todd, 2000). These qualifications should be kept in mind when interpreting twin data. The point-estimates of heritability derived from twin studies should be seen as only estimates and are usually reported along with their confidence intervals.

Neurogenetics

For 2 decades, the workhorse of human genetics has been genetic linkage combined with positional cloning. This strategy has been remarkably successful in identifying genes for rare Mendelian disorders (Risch, 2000). However, genes contributing to common disorders characterized by multiple genes and small effect sizes are more difficult to reliably identify. Similarly, genes underpinning quantitative phenotypes have also proved elusive.

The application of population- and family-based candidate gene strategies has scored some successes but many nonreplications. In the past several years, genome wide association (GWA) studies (Hardy and Singleton, 2009; Ioannidis et al., 2009), using high-throughput microarray platforms and genotyping large numbers of subjects, have revolutionized genetic studies and produced promising signals at specific chromosomal loci for complex phenotypes such as type II diabetes (Lango et al., 2008), rheumatoid arthritis (Wellcome Trust Case Control Consortium, 2007), human height (Weedon et al., 2008), and mental illness (Allen et al., 2008; Brookes et al., 2006; Gershon et al., 2008; Treutlein et al., 2009). The power of GWA is that it is not hypothesis driven and samples the entire genome in the analysis. Single-nucleotide polymorphism (SNP) frequencies are compared across cohorts or quantitative phenotypes to ascertain chromosomal regions that partially explain the phenotypic variance.

Although GWA has become one of the most important strategies in identifying genes contributing to complex human traits, the high-throughput chip technology—by allowing the examination of hundreds of thousands to more than a million SNPs—generates a problem of multiple testing. Sorting out false-positive association signals and reducing false-negative ones is a crucial challenge for GWA studies (Vineis et al., 2008). However, statistical methods to address this issue that are also applicable to multiple hypothesis testing are being continually developed (Gao et al., 2009; Jensen et al., 2009; Kang et al., 2009).

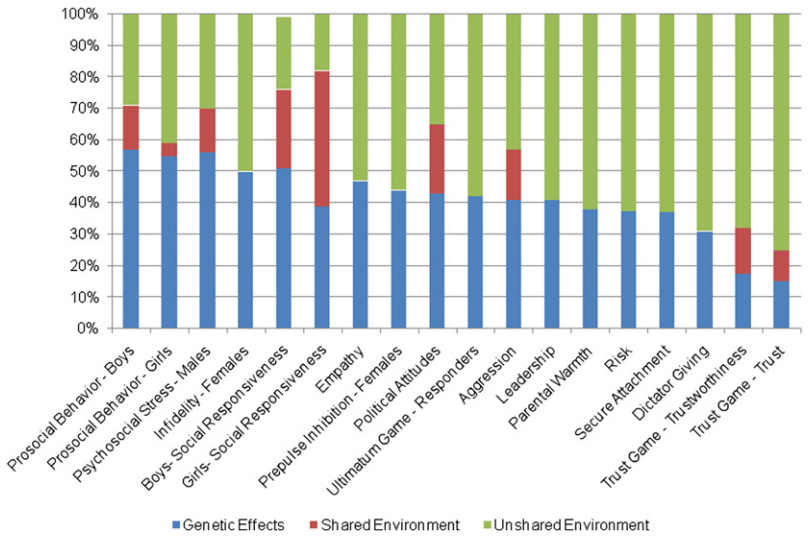

Figure 3. Heritability of Social Behavioral Phenotypes

The relative influences of genetic effects (both additive and dominant), the shared environment, and the unshared or unique environment (which also includes measurement error) in contributing to social phenotypes. Phenotypes are listed in order of estimated genetic effects, with descriptions and references provided in Table S2.

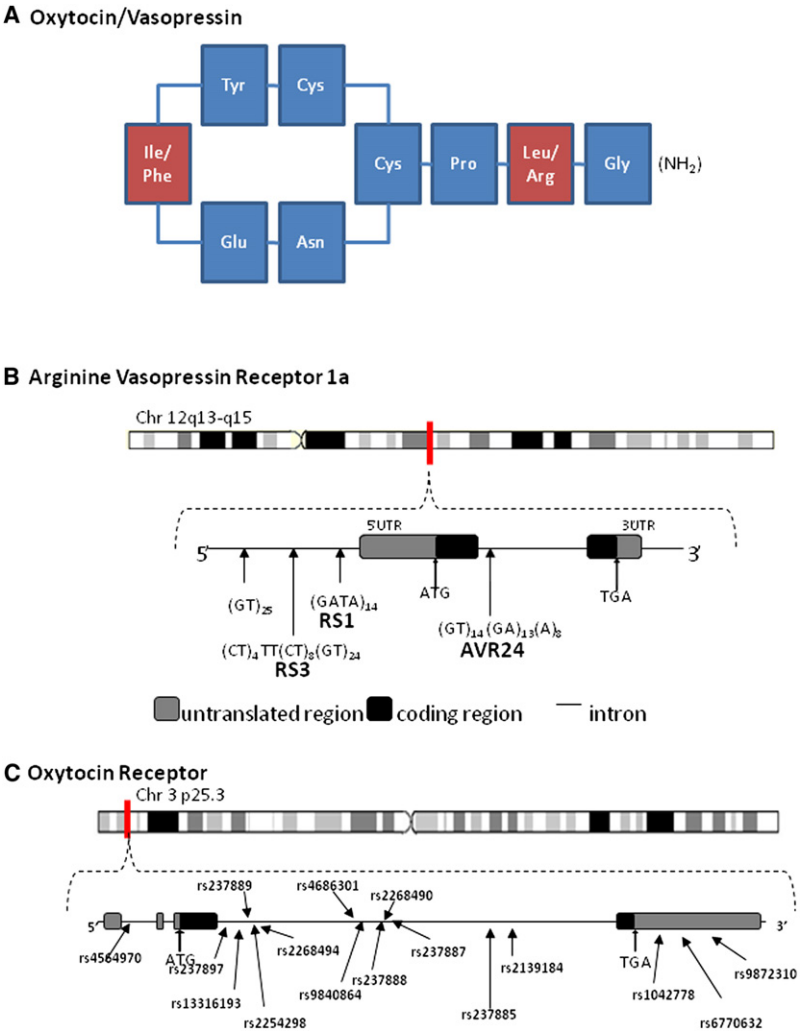

Figure 4. Vasopressin/Oxytocin Schematic, and Genetic Variation (SNPs) across the *OXTR* and *AVPR1a* Genes

(A) The nonapeptides OT and AVP differ in two amino acids. (B) *AVPR1a* has two exons and three repeat regions: two in the promoter region (RS1 and RS3) and one intronic repeat. (C) The *OXTR* contains three introns and four exons. Several dozen SNPs have been identified within the gene, and the figure shows only tagging SNPs obtained from the HapMap database and Haploview program. A tagging SNP is a representative SNP in a region of the genome with high linkage disequilibrium (the nonrandom association of alleles at two or more loci). It is possible—and also cost-effective—to capture most of the genetic variation without genotyping every SNP in a chromosomal region.

Independent replication is a crucial step in validating both GWA studies and candidate gene investigations. In this review, we underscore whenever studies have been replicated and, importantly, if they have been further analyzed by meta-analysis. By pooling data from independent studies, meta-analysis is a crucial step in establishing the credibility of genetic associations. Interim guidelines have been set by the Human Genome Epidemiology Network (HuGENet) (http://www.cdc.gov/genomics/hugenet/) that are designed, in part, to facilitate subsequent meta-analyses. A good example of the application of this technique to a behavioral phenotype is the recent analysis of candidate gene studies in schizophrenia (Allen et al., 2008). In addition, the findings of an interaction between monoamine oxidase A (*MAOA*) genotype and antisocial behavior (Caspi et al., 2002) were substantiated following meta-analysis (Taylor and Kim-Cohen, 2007), despite the absence of a main effect of *MAOA* on such behavior. An interesting application of the meta-analysis approach is the demonstration that the association of the serotonin transporter promoter-region *5-HTTLPR* polymorphism and amygdala activation is not only significant, but accounts for 10% of the phenotypic variance (Munafò et al., 2008a).

Neurogenetic approaches are a powerful tool in the identification and verification of the neurotransmitter pathways and brain regions that underlie social behavior, and this approach may be especially potent when coupled with functional imaging (Esslinger et al., 2009). Finally, since some social phenotypes can be straightforwardly inventoried in large numbers of subjects (via surveys, online game playing, and vast reservoirs of sociodemographic data), we predict that operationalization of the GWA platform for many, but perhaps not all, facets of human social behavior is just a matter of time.

Oxytocin and Arginine Vasopressin Influence Social Behavior

The neuropeptides oxytocin (OT) and arginine vasopressin (AVP) share a long evolutionary history and are two of the most-studied brain signaling molecules encoding information relevant to social behavior. These nonapeptides share a similar chemical structure (Figure 4A) and play a key role across vertebrates in molding social interactions (Carter et al., 2008; Heinrichs and Domes, 2008). The best characterized AVP receptor from the vantage point of social behavior is *AVPR1a*, which has several repeat regions that have been examined for their association with human social behavior (Israel et al., 2008) (Figure 4B). For example, the dramatic differences in social behavior between the closely related prairie vole and meadow vole have been linked to the length of the AVP receptor *AVPR1a* repeat regions (Hammock, 2007). There is accumulating evidence that AVP and OT also fulfill a role as social hormones in humans.

Prepulse inhibition (PPI) of the startle response is a largely autonomic response that resonates with social cognition in both animal models (Dieckmann et al., 2007) and humans (Wynn et al., 2005) An efficient analysis of reality, including social reality, depends upon the capacity to ignore or inhibit perceptions of some of these stimuli (Braff et al., 2001). Longer *AVPR1a* RS3 alleles are associated with greater levels of PPI (Levin et al., 2009), particularly in males. This observation is consistent with

a role for the promoter repeat region in partially molding social behavior in both animals and humans. Knafo et al. (2008a) likewise demonstrated that in human postmortem hippocampus, *AVPR1a* mRNA levels were higher in specimens with the long/long compared to the short/short RS3 genotype. Additionally, recent work demonstrating a correlation between the *AVPR1a* RS3_334 bp allele and differential overactivation of the left and right amygdala (significant on the left) when viewing threatening faces supports the role of AVP in emotional processing (Meyer-Lindenberg et al., 2008). This combined evidence supports the proposal that microsatellites in the *cis*-regulatory regions of *AVPR1A* gene have relevance for brain function related to emotional arousal and social behavior.

AVPR1a and *OXTR* show provisional association not only with normal social behavior but also with altered social function. *AVPR1a* has been associated with autism (Yirmiya et al., 2006), a disorder characterized by a core deficit in social interactions, and an association between SNPs across the *OXTR* gene and autism has also been reported (Jacob et al., 2007; Lerer et al., 2008; Wu et al., 2005). By genotyping all htSNPs across the *OXTR* gene region (Figure 4C), Lerer et al. (2008) observed an association between SNPs/haplotypes and measures of social skills in affected individuals. Interestingly, one SNP (rs2254298) was significantly associated with autism across all three studies as well as in a study of prosocial behavior in nonclinical subjects (Israel et al., 2009).

Personality Genetics

A seeming point of departure for studying the genetics of social cognition is personality genetics, a field that has blossomed in the past 2 decades (Ebstein, 2006). Rather than focusing on the genetics of the classic personality traits that have been extensively reviewed and subjected to meta-analysis (Kluger et al., 2002; Munafò et al., 2008b, 2008c; Risch et al., 2009), we focus on what we consider "emerging" areas of research in social cognition that have only recently begun to be studied with molecular genetics.

Prosocial Behavior

> *"Inveterately altruistic creatures have a pathetic tendency to die before reproducing their kind."* —W.V. Quine, on the evolutionary paradox of altruism

Early twin studies indicated the importance of genes in contributing to human prosocial behavior (Rushton, 2004; Rushton et al., 1984). Broad heritabilities (56%–72%) were observed in adult twin pairs for self-reported measures of altruism, empathy, and nurturance, with only a negligible effect of the shared environment (Rushton et al., 1984). More recent studies have taken a developmental perspective and have examined heritability of prosocial traits and empathy in children across a wider age range in the hopes of identifying more systematic developmental patterns (Knafo, 2006; Knafo and Israel, 2009; Knafo and Plomin, 2006a, 2006b; Knafo et al., 2008b). A consistent pattern of results has emerged, in which genetics and nonshared environment effects become increasingly important, and shared environment effects decrease in importance as children move from early childhood to middle childhood.

Empathy

> *"The great gift of human beings is that we have the power of empathy."* —Meryl Streep

A prerequisite for successful social interactions and mental well-being is empathy, the ability to share the other's feelings (Hein and Singer, 2008). The developmental emergence of empathy was studied by Knafo and colleagues (Knafo et al., 2008b), who examined the contribution of genes and environment to an empathy factor in 409 pairs of young twins. No genetic influences were found at 14 and 20 months, while strong shared environmental influences accounted for most of the variance. However, at 24 and 36 months, genetics accounted for 34%–47% of the variance in the common empathy factor, while shared environment effects decreased from 0.69 at 14 months to 0 at 36 months. Overall, genetics accounted for both change and continuity in empathy, but their role changed as children grew up. In another twin study at 3.5 years of age, moderate heritabilities were estimated for individual differences in empathy, and the rest of the variance was accounted for by nonshared environment (Knafo et al., 2009).

In a recent study designed to examine the role of specific genes contributing to empathy (Rodrigues et al., 2009), the authors tested a single intronic *OXTR* SNP, rs53576, previously associated with autism (Wu et al., 2005) and maternal sensitivity (Bakermans-Kranenburg and Van IJzendoorn, 2008). Compared with individuals homozygous for the G allele of rs53576 (GG), individuals with one or two copies of the A allele (AG/AA) exhibited lower behavioral and dispositional empathy.

Social Stress

Aggression and social stress are essential components of the behavioral repertoire of all animals, and neither animals nor humans would long survive in their absence. It seems a reasonable notion that some form of aggression is a key to success in the competitive modern era (Coates et al., 2009). That said, excess social stress and aggression are assuredly detrimental both to the individual and society.

Social contact more often than not has stressful consequences. Gender-sensitive individual differences in stress reactivity to some extent account for long-term adaptation and well-being (Solomon and Herman, 2009), and dysregulation of the stress response is a risk factor for many psychological disorders such as depression and anxiety. Genetic vulnerability plays a role in stress adaptation (Wüst et al., 2005). Individual differences in responses to the Trier Social Stress Test are partially attributed to polymorphic differences in the glucocorticoid receptor gene (Wüst et al., 2004). Additionally, developmental genes such as brain-derived neurotrophic factor were shown to modulate, in a gender-specific manner, hypothalamic-pituitary-adrenal axis response to social stress evoked by the test (n = 97) (Shalev et al., 2009).

Aggression

> *"The tendency to aggression is an innate, independent, instinctual disposition in man…"* —Sigmund Freud

Twin and family studies suggest that over 50% of the variance in aggressive traits is accounted for by heredity (Craig and Halton,

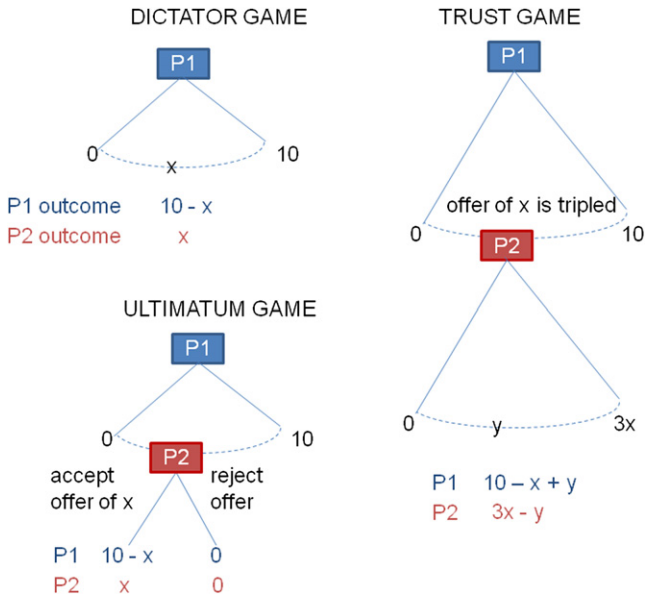

Figure 5. Games in Play in Experimental Economics
The dictator (Forsythe et al., 1994; Kahneman et al., 1986), ultimatum (Guth et al., 1982), and trust (Berg et al., 1995) games. Games have been widely studied in the emerging field of neuroeconomics (Fehr and Fischbacher, 2003). These games illustrate fundamental concepts of dyadic social interactions including fairness, altruism, and preferences for equity.

2009). There is a well-known gender distinction in aggressive behavior, but the relationship between individual androgen levels and an individual's aggressive behavior in humans remains equivocal. A particularly attractive explanation of the less than robust correlation of baseline androgen levels with individual measures of aggressive behavior is the "challenge hypothesis," which suggests that testosterone rises in the face of a challenge and activates behaviors intended to dominate and enhance status (Archer, 2006). For example, high levels of testosterone are linked with dominance and competitiveness in human males (Burnham, 2007). The reader is referred to the excellent review of Craig and Halton (2009) for a thorough discussion of additional potential candidate genes for contributing to human aggression.

Popularity

> *"Popularity is the easiest thing in the world to gain and it is the hardest thing to hold."* —Will Rogers

The first study that identified a specific polymorphism associated with popularity was by Burt (2008). Subjects rated one another on popularity after a sham social encounter, and the data was analyzed using a two-way random-effects social relations model that allowed for the capturing of evocative components of peer selection and popularity. A promoter-region SNP in the serotonin receptor 2A (*HRT2A*) was significantly associated with popularity, accounting for 5% to 8% of its variance. Similar results were obtained in two samples (n = 127 and 88, all male). While future research should examine other polymorphisms in larger samples that include females, this provisional finding is an example of an evocative gene environment correlation whereby individuals' genes predispose them to particular social outcomes (Plomin et al., 2008).

Social Decision Making through the Lens of Experimental Economics

The pencil and paper approach to personality genetics is gradually being complemented by incentivized laboratory-based paradigms (Dreber et al., 2009; Israel et al., 2009; Knafo et al., 2008a; Kuhnen and Chiao, 2009; Zhong et al., 2009a, 2009b), sometimes powerfully combined with brain imaging (Buckholtz et al., 2008), which are generating deep insights into the neurobiological-neurogenetic structure of social cognition. An emerging field of research capitalizing on rigorous experimental economic paradigms combined with cutting-edge neuroimaging technology is revolutionizing our understanding of human decision making and social interactions (Fehr and Camerer, 2007) and opening new vistas for understanding social behavior in both nonclinical groups (de Quervain et al., 2004; Sanfey et al., 2003) and clinical groups (Chiu et al., 2008; King-Casas et al., 2008). There is an emerging literature combining experimental economics and behavioral genetics approaches to explore the genetic basis of economic decision making. Figure 5 depicts games commonly employed in behavioral economic experiments.

Notably, individual differences in prosocial behavior modeled by economic games are partially explained by common polymorphisms in *AVPR1a* and *OXTR*. In the dictator game (DG), the "Dictator" makes a unilateral decision regarding the distribution of a fixed sum of money between herself and the second player, the "Recipient." Because the recipient is completely powerless, allotment of money by the dictator can be seen as a measure of pure altruism (Forsythe et al., 1994; Kahneman et al., 1986). The literature on DG behavior reveals that dictators tend to give around 20% of their endowment (Camerer, 2003). A recent study focused on uncovering specific genes that partially explain individual differences in the extent of giving demonstrated that allocation of money was related to the length of the *AVPR1a* RS3 promoter repeat (Knafo et al., 2008a). In a second study (Israel et al., 2009), association was also observed between tagging SNPs across the *OXTR* receptor region for both the DG and a second related paradigm, Social Value Orientations (SVO) (Van Lange et al., 1997). In the SVO, individuals make a set of decisions regarding the outcome of money for themselves and an anonymous other. Each outcome relates to a different value orientation (cooperative, individualistic, or competitive) used to describe the participant's motivational preference.

Another well-known experimental economic game paradigm, the ultimatum game (UG), directly addresses the trade-off between fairness preferences and selfish motives. In the UG, the first participant proposes a split of a sum of money, while the second subject decides whether to accept. If the proposal is not accepted, the players receive no money. If the decision is based solely on selfish motives, the first subject will make a minimal offer, anticipating that the second player will find any positive amount acceptable. However, proposals tend to be fairly close to 60-40, and responders tend to reject proposals offering less than 30% of the given amount (Camerer, 2003). A recent twin study with 658 participating individuals including

71 DZ and 258 MZ pairs of twins reported the heritability of responder behavior at 42%. It did not report heritability of proposer behavior, citing a lack of variation (Wallace et al., 2007).

The trust game is a widely employed paradigm to model cooperative behavior as measured by interpersonal trust and willingness to reciprocate trust (Berg et al., 1995). In the trust game, an individual (the investor) decides how much money out of an initial endowment to send to another subject (the trustee). The sent amount (a measure of trust) is then multiplied by some factor, usually three, and the trustee decides how much of the money received to send back to the investor (trustworthiness). In a large twin study, Cesarini et al. (2008) inventoried subjects independently recruited in either the United States or Sweden. Heritability estimates for trust were 20% in the Swedish experiment and 10% in the US, and heritability estimates for trustworthiness were 18% in the Swedish sample and 17% in the American sample. The remainder of the variance was accounted for by nonshared environmental factors and error. The study is notable for obtaining heritability estimates in two independent samples.

Despite the increasing use of experimental economic paradigms as a basis for understanding many facets of social cognition, issues have been raised regarding the validity of such paradigms and their relationship to the real world. Further objections to using laboratory experiments include extensive use of student participant pools, which are unrepresentative of the general population and are small sample sizes. Nevertheless, the great strength of laboratory experiments is that they provide controlled variation, the bedrock of experimental science, and these experiments complement other approaches such as field experiments and surveys. To increase their validity and improve their ability to predict outcomes, economic preference measures should be subject to the same psychometric standards as personality measures, including evidence of internal reliability, test-retest stability (over short periods), convergent validity, discriminant validity, and predictive validity (Borghans et al., 2008). There is surprisingly little evidence of test-retest stability in economic experiments (Cesarini et al., 2009), an issue that deserves more attention.

The Rich Contours of Human Social Behavior

In the world beyond the laboratory, humans are engaged in a wide range of interactive social behaviors, many of which acquire forms unique to our species. With respect to intensity and time invested, parenting is unique in humans, and pursuits such as political activity, music, and language acquisition are also intensely human. Remarkably, there is evidence that these phenotypes show considerable heritability, and some have been associated with specific genes.

Parenting

> *Every beetle is a gazelle in the eyes of its mother.* —Arab proverb

Our earliest exposure to empathy is parenting. Indeed, parental care may have been the evolutionary drive behind the development of empathy, which could then be extended to nonkin. A role of empathy has been suggested in animal behavior, suggesting that human empathy may have roots in our evolutionary past (de Waal, 2007). Studies using the twins-as-parents design have shown that parenting is partly heritable. For example, Losoya et al. (1997) reported a correlation of 0.60 for MZ twin parents' support of their 8-year-old children, as compared with a 0.30 correlation for DZ twin parents. Kendler (1996) found that parental warmth was heritable (0.38), but parental authoritarianism and protectiveness were not. There is evidence of gene-environment correlations for mothers and fathers on their self-reported parenting with regard to positivity, negativity, monitoring, and control (Neiderhiser et al., 2004, 2007). Parenting is not a pure environmental measure, nor is it influenced solely by the parent's genotype. Rather, children's genes influence both the way the child is parented, and the child's reaction to that parenting.

Dopaminergic genes are associated with brain reward systems (Schultz et al., 2008), infant attachment (Lakatos et al., 2002; Van IJzendoorn and Bakermans-Kranenburg, 2006), attention deficit hyperactivity disorder (ADHD) (Faraone and Khan, 2006), adult human personality traits (Ebstein, 2006), and temperament in infants (Ebstein et al., 1998). The dopamine system has also been linked to parenting in a recent study demonstrating an association between less efficient alleles of the dopamine D4 receptor (*DRD4*) and the catechol-O-methyltransferase (*COMT*) genes and both daily hassles and less sensitive parenting (van IJzendoorn et al., 2008). Conversely, the most efficient allelic combination appeared to buffer the negative effect of daily hassles on maternal sensitivity. Another well-characterized dopaminergic polymorphism in the dopamine transporter (*DAT1*) was tested for association with maternal parenting behavior (Lee et al., 2008). In two cohorts consisting of 127 ADHD probands and a control group of 126 control children, a significant nonadditive association was found between maternal *DAT1* genotype and both negative parenting and total commands during a structured mother-child interaction task. The association between maternal *DAT1* genotype and negative parenting was significantly stronger among mothers whose children were highly disruptive during the mother-child interaction task, suggesting a gene-environment interaction.

Other polymorphisms in the oxytocin receptor (*OXTR*) and the serotonin transporter *SLC6A4* promoter region 44 base-pair insertion deletion (a.k.a. *5-HTTLPR*) were also tested for possible contribution to individual differences in sensitive parenting toward 2-year-old toddlers at risk for externalizing behavior problems (Bakermans-Kranenburg and Van IJzendoorn, 2008). Controlling for differences in maternal education, depression, and marital discord, parents with the less efficient variants of *SLC6A4 5-HTTLPR* and an *OXTR* SNP (rs53576) showed lower levels of sensitive responsiveness. Additionally, in nonhuman species (Meaney and Szyf, 2005; Mueller and Bale, 2008; Weaver et al., 2004) and humans (McGowan et al., 2009; Oberlander et al., 2008), the impact of parenting and early environment on behavior is mediated by epigenetic changes.

Life History Behaviors

> *Love tastes sweet, but only with bread*. —Yiddish proverb

A spectrum of life history choices and family planning styles (age at first conception, number of children, interest in marrying, the formation of long-term pair bonds, trend for multiple mating

patterns) have been explored in twin studies that, overall, demonstrate a moderate heritability across these phenotypes (Trumbetta et al., 2007). A significant association between the *AVPR1a* RS3-repeat polymorphism and outcome measure inventoried by the Partner Bonding Scale was observed for men, but not for women, in a study of 550 same-sex Swedish twin pairs and their spouses (Walum et al., 2008). These data are consistent with the more prominent influence of vasopressin on social behavior in male voles over that of female voles (Winslow et al., 1993). As discussed above, we also observed association between RS3 and PPI solely in male subjects (Levin et al., 2009), strengthening the notion that across diverse species, though depending on phenotype, this receptor often plays a more prominent role in males than females in social behaviors.

An association has also been observed between *AVPR1a* RS3 and age of first sexual intercourse (Prichard et al., 2007). Men with the long/long genotype showed a trend to have sex before age 15 compared with those harboring the short/short genotype. Interestingly, an association was also observed between the *AVPR1a* RS1 polymorphism and age of first sexual intercourse in females. Self-reported infidelity and number of sexual partners are both under moderate genetic influence (41% and 38% heritable, respectively), and the genetic correlation between these two traits is strong (47%) (Cherkas et al., 2004). Surprisingly, attitudes (but not the act itself) toward infidelity are driven by shared and unique environmental, but not genetic, influences. A genome-wide linkage scan identified three suggestive linkage areas associated with infidelity and number of sexual partners, but the investigators were unsuccessful in associating infidelity or number of sexual partners with the *AVPR1a* gene region (Cherkas et al., 2004). Associations of a microsatellite marker (Michelini et al., 1995) near the *OXTR* gene were also observed for sexual and reproductive behavior (Prichard et al., 2007). Females with the long/long genotype were significantly less likely to use oral contraception and were more likely to have children.

There is converging evidence that the boundary between OT and AVP and dopaminergic reward circuits is of special significance for molding the social brain (Skuse and Gallagher, 2009). Indeed, the *DRD4* receptor, which has been linked to altruistic behavior (Bachner-Melman et al., 2005b), is also associated with sexual behavior (Ben Zion et al., 2006). Interestingly, a relationship between sexual attitudes and the *DRD4* receptor was also observed in a longitudinal study of adolescent health that examined 305 pairs of MZ twins and 269 pairs of same-sex DZ twins (Guo and Tong, 2006). However, this study was characterized by considerable ethnic heterogeneity, possibly confounding interpretation of the results. Additionally, Eisenberg et al. (2007) reported that individuals with *DRD4.7* repeat alleles were more likely to have had sexual intercourse and to desire children earlier in life. These individuals were also more likely to report multiracial ancestries, perhaps strengthening the connection between this gene and patterns of human migration (Chen et al., 1999). In contrast, individuals with *DRD2* A1 alleles were more likely to not want children and not want to marry. Dopamine and serotonin are also linked to human romantic bonding (Emanuele et al., 2007). The association between genes encoding elements of dopaminergic neurotransmission and human sexuality and romantic attachment as well as parenting styles makes good biological sense in light of the role of dopamine in driving brain reward mechanisms (Schultz, 2004), specifically in sexual behavior (Paredes and Agmo, 2004). Moreover, the involvement of *AVPR1a* in "love and marriage" is congruent with animal (Smeltzer et al., 2006) and human (Scantamburlo et al., 2005) studies that show an interaction between vasopressin and brain dopamine circuits.

Leadership

> *"It's hard to lead a cavalry charge if you think you look funny on a horse."* —Adlai Stevenson

Arvey and his colleagues assessed leadership in 650 male MZ and DZ twins from a role occupancy perspective, where leadership is defined and measured in terms of the various formal and informal leadership role attainments of individuals in work settings (Arvey et al., 2006). Results indicated that 30% of the variance in leadership role occupancy could be accounted for by genetic factors, while nonshared environmental factors accounted for the remaining variance in leadership role occupancy. Genetic influences also contributed to personality variables known to be associated with leadership, such as social potency and achievement. Moderate heritability of leadership occupancy has also been observed in women (Arvey et al., 2007).

Politics

> *"Man is, by nature, a political animal."* —Aristotle

A recent review (Fowler and Schreiber, 2008) discusses the evidence that some of our most cherished political beliefs and behaviors may have a genetic basis. Twin studies have suggested that liberal and conservative ideologies are heritable, albeit genes did not play a role in the choice of any particular political party (Alford et al., 2005; Hatemi et al., 2007). Further investigations showed that genes and environment jointly contributed to political behavior (Fowler et al., 2008). Interestingly, value priorities (basic personal values referring to the broad goals to which people attribute importance as guiding principles in their lives, e.g., tradition, benevolence, hedonism) have been shown to underlie political attitudes and behaviors (Caprara et al., 2006; Nir and Knafo, 2009). Recent research shows that value priorities are moderately (11%–38%) heritable (Schermer et al., 2008).

Recent work has been aimed at identification of specific candidate genes contributing to political behavior. Fowler and colleagues hypothesize that genes may influence voting and political participation because they influence a generalized tendency to engage in prosocial behavior via their functional role in neurochemical processes (Fowler, 2006; Fowler and Kam, 2007). Studies utilizing DGs to measure revealed social preferences show that individuals who are more willing to engage in costly giving to others are also more likely to vote and participate in politics (Fowler, 2006). Genes that are prima facie candidates for contributing to voting behavior due to their association with social behaviors include *SLC6A4* (Lesch, 2007), *MAOA* (Caspi et al., 2002), and *DRD2* (Noble, 2003). Indeed, in a large association study, voter turnout was associated with the *MAOA* promoter region repeat, and a gene × environment

interaction was indicated between the serotonin transporter and those who frequently participated in religious activities (Fowler and Dawes, 2008). The odds of voting among those who carry the "long" version of the *SLC6A4* 5-HTTLPR promoter repeat, corresponding to high transporter activity, and who frequently attend religious services, are 1.58 greater than for people with the "short" version. A dopaminergic involvement is also suggested because voter turnout was associated with the *DRD2* gene, where TaqI A2 carriers were significantly more likely to identify as partisans with a particular political party than A1 carriers were (Dawes and Fowler, 2009). This work is preliminary and replication will be crucial, but it suggests that neurotransmitter function has an effect on political behavior.

Music

> *"Music is the universal language of mankind."* —Henry Wadsworth Longfellow, *Outre-Mer: A Pilgrimage Beyond the Sea*

A difficult question tackled by Fitch (2006) in his cogent review of music and evolution is, "Why music?" Indeed, Darwin noted: "As neither the enjoyment nor the capacity of producing musical notes are faculties of the least use to man in reference to his daily habits of life, they must be ranked amongst the most mysterious with which he is endowed." One explanation is that music is a byproduct of some other capacity such as language, but is not specifically adaptive in itself (Gould and Lewontin, 1979). Others have suggested that music and dance have adaptive value in group adhesion, mother-infant bonding, and even as a form of play (Fitch, 2005, 2006; Mithen, 2009). Undoubtedly, the adaptive significance of music evolution in our species will be difficult to resolve, but the search for genes that influence music has a fascination in its own right.

One strategy to identify candidate genes for music cognition is to look to other vertebrates that employ music as an effective mode of signaling. Intriguingly, the vasopressin peptidergic signaling system plays a role in musical signaling across vertebrates including fishes (Goodson et al., 2003), mice (Bleickardt et al., 2009; Scattoni et al., 2008; Winslow and Insel, 1993), and birds (Goodson, 2008). The *AVPR1a* gene is a likely candidate for coding some facets of the music phenotype. In a first study of its kind, highly significant differences in *AVPR1a* haplotype frequencies, especially when conditional on both *SLC6A4* polymorphisms, were observed between dancers and athletes (Bachner-Melman et al., 2005a). In family-based and population-based tests, highly significant epistatic interactions have also been observed between promoter region polymorphisms in the *AVPR1a* and *SLC6A4* genes and musical and phonological memory (Granot et al., 2007). Ukkola et al. (2009) analyzed polymorphisms of *AVPR1a*, *SLC6A4*, *COMT*, *DRD2*, and tryptophan hydroxylase 1 (*TPH1*) in 19 multigenerational families (comprising 343 members) with professional musicians and/or active amateurs, and found that creative functions in music have a strong genetic component.

Future Directions

The mechanism by which environmental influences impinge on the expression of complex behavioral phenotypes has become the focus of intense research in the past decade. Gene × environment interactions and gene × environment correlations will potentially explain an increasing percentage of the variance in the human social phenotypes (Belsky et al., 2009; Rutter et al., 2006). It therefore behooves future research to inventory environmental information, whenever feasible, toward fully appreciating the neurogenetic mechanisms underlying the social phenotype. Association designs toward deciphering the human social phenotype also need to take advantage of the great advances made in GWA studies employing large numbers of subjects, high-throughput chip technology, and sophisticated statistical analyses (Ioannidis et al., 2009; Neale and Purcell, 2008). However, as attractive as the GWA strategy is in many fields, the logistics of employing laboratory-based assessment of phenotypes to inventory thousands of subjects are daunting.

A promising future direction in genetic research on human social behavior is related to the recent discovery (Iafrate et al., 2004; Sebat et al., 2004) of copy number variations (CNV)—sequences of DNA from 1 kb to several megabases that are either gained or lost when at least two individual genomes are compared. Such variations, readily detectable using microarray technology, often arise de novo and have been associated with complex mental disorders including autism and schizophrenia (Cook and Scherer, 2008). Such variations are likely to be increasingly observed to partially contribute to "dimensional" phenotypes (QTLs) that characterize many social behaviors in both clinical and nonclinical groups (Cook and Scherer, 2008).

The small effect size of most genes so far identified that contribute to common diseases suggests that many genes, as well as the environment, are likely to contribute to social human behavior. Clearly, new data mining techniques, statistical methods, and faster computers will be required to analyze future studies, which are likely to include information from thousands of individuals. As noted in a recent review (McKinney et al., 2006), traditional statistical methods are not well-suited for detecting such interactions, especially when the data are high dimensional (many attributes or independent variables) or when interactions occur between more than two polymorphisms. New directions would possibly include machine-learning models and algorithms for identifying and characterizing susceptibility genes in common, complex, and multifactorial human diseases. Machine-learning methods such as neural networks, cellular automata, random forests, and multifactor dimensionality reduction may be key future developments needed to detect gene × gene interactions.

One of the most promising techniques in the toolbox of neuroeconomics is the use of functional imaging or fMRI. Indeed, as cited throughout this article, imaging techniques have elucidated many facets of human social cognition including empathy (Decety and Sommerville, 2003), charitable giving (Harbaugh et al., 2007), altruism (Fehr and Rockenbach, 2004; Rilling et al., 2004b), trust (Krueger et al., 2007), cooperation (Rilling et al., 2002, 2007), Theory of Mind (Frith and Frith, 2006; Rilling et al., 2004a; Singer et al., 2006), altruistic punishment (de Quervain et al., 2004), and sense of fairness as modeled in the UG (Sanfey et al., 2003).

Future studies will undoubtedly further expand in the direction of imaging genomics (Hariri and Weinberger, 2003) combined with pharmacogenomics, fields where much progress has

been made and which have great future potential (Grassi et al., 2008). Finally, the important new strategy of using experimental economic paradigms, especially when combined with pharmacological, imaging, and neurogenetic approaches, can provide valuable insight into the multiple facets of human social behavior.

The past 2 decades have seen remarkable progress in unraveling the complexities of the neurogenetic architecture of the human social brain. Nevertheless, much remains to be learned, especially about how our species has created a global society composed of billions of interacting individuals whose basic brain structure has remained mostly unchanged for the past 50,000 years. This global society is indeed a remarkable achievement for an organ weighing only 1350 g, and attests to its remarkable plasticity in processing a continuous stream of environmental information using neuroanatomical and neurogenetic mechanisms laid down over millions of years of hominid evolution.

SUPPLEMENTAL INFORMATION

Supplemental Information for this article includes two tables and can be found with this article online at doi:10.1016/j.neuron.2010.02.020.

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